Seizure (2006) **15**, 292–298

ELSEVIER

SEIZURE

www.elsevier.com/locate/yseiz

Open prospective study on oxcarbazepine in epilepsy in children: A preliminary report

E. Franzoni [a,*], C. Garone [a], J. Sarajlija [a], S. Gualandi [b], E. Malaspina [a], I. Cecconi [a], F.C. Moscano [a], V. Marchiani [a]

[a] *Child Neuropsychiatry Unit, Bologna University, Italy*
[b] *Clinical Pediatrics, Bologna University, Italy*

Received 3 November 2005; received in revised form 16 January 2006; accepted 17 February 2006

KEYWORDS
Children;
Epilepsy;
Oxcarbazepine;
Efficacy;
Tolerability

Summary

Purpose: To evaluate the long-term efficacy, tolerability, and safety of oxcarbazepine (OXC) in children with epilepsy.
Methods: We enrolled 36 patients (median age 7.75) with new diagnosis of partial epilepsy in an open prospective study. All type of epilepsy were included: 25 patients were affected by idiopathic epilepsy, eight by symptomatic epilepsy and three by cryptogenic epilepsy. Patients were then scheduled to come back for controls at 3 months (T1), 12 months (T2) and 24 months (T3) after the beginning of OXC-monotherapy (T0). At each control we evaluated patients through their seizure diary, a questionnaire on side effects, their level of 10-monohydroxy (MHD) metabolite and laboratory analysis.
Results: At T1, 21/36 patients (58.3%) were seizure-free, 3/36 patients (8.3%) showed an improvement higher than 50%, 3/36 (8.3%) lower than 50%, while 2/36 worsened (5.6%). In 7/36 (19.5%) patients, no improvement was reported. At T2 13/18 patients (72.2%) were seizure-free, 1/18 showed a response to therapy higher than 50% while 2/18 worsened (11%). In two patients no improvement was reported. A correspondence between MHD plasmatic levels and clinical response ($r = 0.49$; $p < 0.05$) was only registered at T1.

An EEG normalization was observed in 25% of cases. Side effects were reported in 25% of cases, but symptoms progressively disappeared at follow-up.
Conclusions: We can therefore conclude that OXC can be considered, for its efficacy and safety, as a first line drug in children with epilepsy.

* Corresponding author at. Via Massarenti 11-40138 Bologna, Italy. Tel.: +39 0516363653/346744; fax: +39 051304839.
E-mail address: emilio.franzoni@unibo.it (E. Franzoni).

1059-1311/$ – see front matter
doi:10.1016/j.seizure.2006.02.017

Introduction

Oxcarbazepine (OXC) is a keto-analogue of carbamazepine (CBZ), with a similar spectrum of activity and anticonvulsant efficacy, but its pharmacokinetic, safety and tolerability profiles seem to be more favorable than its analogue.[1–4]

OXC is metabolized primarily through reductive bio-transformation and conjugation (glucuronidation) to the active 10-monohydroxy derivate (MHD) that is the main active metabolite.[5] Moreover, it has a low propensity to inhibit or induce oxidative enzymes and has a small potential for drug–drug interactions.

OXC is a second-generation antiepileptic drug (AED), with proven efficacy as monotherapy[6–8] and combination therapy[9] for the treatment of partial seizures (including subtypes of simple, com-

Table 1 Study design: timing of enrolment patients and discontinuation/completion treatment

		T1	↑mg/kg	T2	↑mg/kg	T3	Seizure-free for 2 years
January–March 2003	N	6		6		5	
	SF	3		3		4	2
	R	0	3	1	2	0	
	NR	3		2		1	
	E	0		1			
April–June 2003	N	5		5		4	
	SF	3		3		4	3
	R	1		0			
	NR	1	1	2	1		
	E	0		1			
July–September 2003	N	4		2			
	SF	2		2			
	R	0					
	NR	2					
	E	2					
October–December 2003	N	3		3			
	SF	2		3			
	R	0					
	NR	1	1				
	E	0					
January–March 2004	N	4		2			
	SF	1		2			
	R	0					
	NR	3	1				
	E	2					
April–June 2004	N	7					
	SF	5					
	R	2					
	NR	0					
	E	0					
July–September 2004	N	4					
	SF	3					
	R	0					
	NR	1	1				
	E	0					
October–December 2004	N	3					
	SF	2					
	R	0					
	NR	1	1				
	E	0					

N, total number cases investigated; SF, seizure-free; *r*, responder greater 50%; NR, non-responder; E, dropouts; T1, evaluation at 3 months after the beginning of therapy; T3, evaluation at 12 months after the beginning of therapy; T3, evaluation at 24 months after the beginning of therapy.

plex and partial secondarily generalized seizures) in adults[6,10,11] and children with epilepsy.[9,12]

OXC-monotherapy could be initiated at 300 mg/day and titrated at weekly intervals by 300 mg/day.[10]

A previous treatment with carbamazepine can be switched to OXC overnight[13] or can gradually be replaced by OXC,[14] both in add-on and monotherapy. On the contrary, a gradual switch over 2–3 weeks is more appropriate in patients receiving AEDs other than CBZ.[10]

In general, side effects are similar to those of CBZ (gait instability, dizziness, drowsiness, nausea and vomiting, fatigue, headache, ataxia, sedation, hyponatraemia, mild skin rashes, serious hypersensitivity reactions, diplopia) although they tend to be less severe and less frequent.[11,15,16]

This study is an open prospective analysis about efficacy, tolerability and safety of OXC.

Patients and methods

Thirty-six patients were enrolled between January 2003 and December 2004.

Inclusion criteria:

- age $\geq$2 years,
- diagnosis of symptomatic, idiopathic and cryptogenic epilepsy according to the International League Against Epilepsy (ILAE),[17,18]
- partial or complex or secondarily generalized seizures,
- patients not previously treated with antiepileptic drug,
- $\geq$2 seizures in the previous month,
- informed consent by parents and/or caregivers.

Exclusion criteria:

- poor compliance by parents/caregivers,
- myoclonic epilepsy and absence epilepsies,
- generalized epilepsy.

Timing of enrollment is shown in Table 1.

Patients were only treated with OXC and did not receive any other co-medication during the study.

At the following control, if seizures frequency was still high, the dose was increased by 10 mg/kg.

Each patient was scheduled to attend periodic clinical controls the first being 3 months (T1) after the beginning of OXC-monotherapy (T0).

A second check (T2) was made 12 months after since the introduction of OXC (T0); if laboratory analysis, general and neurological examinations were normal and seizure frequency had decreased, the following examinations were performed at 24 months (T3).

At each control (T1, T2, T3) the total number of seizures occurred during follow-up were analyzed by using a seizure diary and side-effects with a questionnaire. In addition, EEG, MHD levels and laboratory analysis, in particular white cells count, electrolytes balance, hepatic functional enzymes and cholestasis indexes were evaluated.

Patients were considered responders when their seizure rate decreased by more than 50% versus baseline.

The last evaluation was performed in May 2005.

At present, 36 patients have been examined at T1, 18 at T2 and 9 at T3.

Statistical analysis

The Statistical Package for Social Science 11.0.1 computer program (SPSS inc., Chicago, IL) was used. For statistical analysis, data distribution was analyzed with skewness and kurtosis coefficients and Kolmogorov–Smirnov test. Data are expressed as median and inter-quartile range (IQR); IQR is the distance between the 25th and the 75th percentile. Statistical significance was assessed using Wilcoxon's matched-pairs signed-rank test and Sperman's rank correlation. All nominally significant results at $p < 0.05$ (two-tailed) were indicated.

The median age of the patients evaluated at T0 was 7.75 (5.7–11.0).

Results

Demographic analysis

We report the results on 36 patients affected by epilepsy: 25/36 (69.5%) with idiopathic epilepsy (rolandic epilepsy in 18 cases, occipital Panayotopoulos epilepsy in two cases and occipital benign infantile epilepsy in five cases), 8/36 (22.2%) with symptomatic epilepsy (Table 3), 3/36 (8.3%) with

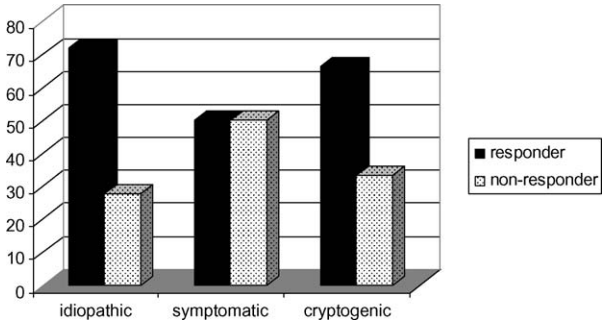

Figure 1 Treatment efficacy in relation to aetiology.

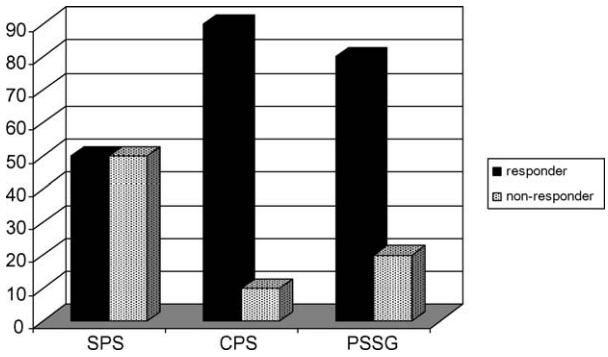

Figure 2 Response to therapy in patients with simple partial seizure (SPS), complex partial seizure (CPS) and secondary generalized seizure (PSSG).

cryptogenic epilepsy (Fig. 1). The type of seizures was simple partial (SPS) in 18/36 cases (50%), complex partial (CPS) in 8/36 (22.2%), secondarily generalized (PSSG) in 10/36 (27.8%) (Fig. 2).

Dose

At T1, patients were taking a median OXC dose of 15.4 mg/kg (10.2—23.5). The median dose was 18.7 mg/kg (12.5—25.5) at T2 and 20.5 mg/kg (16.8—26) at T3 (Table 2).

Plasma levels

At T1, patients reached a MHD-median of 12.8 μg/ml (9.8—15.5). At T2, the MHD median value was 15.3 μg/ml (11.7—21.6) (Table 2). The results of the analysis showed a statistically significant correlation between MHD plasmatic levels and the dose expressed in mg/kg ($r = 0.62$; $p < 0.0001$). At T1, a correspondence between MHD plasmatic levels and reduction of seizures ($r = 0.49$; $p < 0.05$) was reported. At T2 and T3, we could not confirm this statistic correlation because of a smaller number of samples available.

Efficacy

At T1, 21/36 patients (58.3%) were seizure-free, 3/36 patients (8.3%) showed a reduction of seizures higher than 50%, 3/36 (8.3%) lower than 50%, while 2/36 worsened (5.6%). In 7/36 (19.5%) of patients, no improvement was reported. In the non-responder group, rolandic epilepsy was diagnosed in seven patients, symptomatic epilepsy in nine cases and cryptogenic epilepsy in one case. In this group the dose was increased at T1 but only two cases of rolandic epilepsy, two cases of symptomatic epilepsy and one case of cryptogenic epilepsy reached T2 control.

At T2 total amount of responders increased to 77.7% (14/18), with seizure-free percentage of 72.2% (13/18).

One patient with occipital epilepsy experienced a reduction in seizure rate major than 50%. Two patients showed a clinical worsening (10%) and in two patients no improvement was reported. In this group two patients suffered from rolandic epilepsy and two patients from symptomatic epilepsy.

We have observed one child affected by rolandic epilepsy who showed a worsening at T1 and became seizure-free at T2. On the contrary, one child affected by symptomatic epilepsy with SPS resulted seizure-free at T1, but worsened at T2.

Only nine patients reached T3 control (Table 1). Given the small number of subjects, statistical analysis was not performed. The responder percentage was 72% (18/25) in idiopathic epilepsy (Fig. 1). Among these, rolandic epilepsy is diagnosed in 10 patients and occipital epilepsy in seven patients. Therefore, 10/18 patients with rolandic epilepsy and all patients with occipital epilepsy responded to therapy.

Eight patients with rolandic epilepsy did not respond to therapy.

Responders were 4/8 (50%) among patients affected by symptomatic epilepsy and 2/3 (66.6%) among patients affected by cryptogenic epilepsy (Fig. 1). Diagnosis of symptomatic epilepsy are summarized in Table 3.

9/18 (50%) patients with SPS, 7/8 (90%) patients with CPS and 8/10 (80%) patients with PSSG responded to therapy (Fig. 2).

EEG

A good improvement in patients with previous focal abnormalities was reported at T1. A normalization of EEG was observed in 25% of the cases. Abnormalities remained unmodified in 75% of the cases. No EEG focal abnormalities became generalized after drug onset. When the abnormalities were multifocal

Table 2 Age, dose (mg/day) and plasma levels (μg/ml) median at T1 and T2

	Age	mg/day	mg/kg	μg/ml
T1	8.2 (5.7—12.1)	300 (300—450)	15.4 (10.2—23.5)	12.8 (9.8—15.5)
T2	10 (7.7—13.5)	600 (450—600)	18.7 (12.5—25.5)	15.3 (11.7—21.6)
T3	10.5 (8.6—14.2)	675 (600—900)	20.5 (16.8—26)	15.1 (10.9—21.7)

Table 3 Diagnosis in patients with symptomatic epilepsy

N = 8	Diagnosis
Responders	
1	Brain abscess
1	Perinatal lesion
1	Heterotopia
1	Cerebral infantile paralysis
1	Temporal right neoplasia
Non-responders	
1	Herpes encephalitis
1	Post-surgical lesion
1	Dandy—Walker Syndrome

at diagnosis, no differences were reported at the following EEG controls.

Side effects

At T1, side effects were reported in 25% of the cases (Table 4) and in one case only OXC had to be interrupted due to excessive sedation.

In the remaining cases, the symptoms progressively disappeared at follow-up.

Laboratory tests

A median of leukocyte quantity resulted equal to 6.99 (5.6—7.9 $\times$ 10^3 μl^{-1}) at various controls.

No case of hyponatraemia was reported as Na^+ levels remained between 137 and 143 meq/l at various controls, whereas K^+ levels were between 4.1 and 5.1 meq/l.

No hepatic dysfunctions were reported.

Table 4 Side effects at T1, T2 and T3 stages

Side effects	Number of cases		
	T1 stage	T2 stage	T3 stage
Dizziness	—	—	—
Gait instability	—	—	—
Drowsiness	—	—	—
Nausea and vomiting	—	—	—
Fatigue	3	1	—
Headache	2	2	1
Ataxia	—	—	—
Sedation	4	1	—
Hyponatremia	—	—	—
Mild skin rashes	1	—	—
Serious hypersensitivity reaction	—	—	—
Diplopia	—	—	—
Memory deficit	—	1	—
Muscular Pain	1	—	—
Hyperphagia	1	—	—
Agitation	1	—	—

Withdrawal

At present, five patients are withdrawing from OXC because they have now been seizure-free for 2 years (T3). Five patients had to stop the treatment for inefficacy at T1 and one for side effects (sedation) at T2. Among these, idiopathic epilepsy was diagnosed in four patients and symptomatic epilepsy in two patients. These six patients did not complete the study. Currently, 69.4% (25/36) of patients is still under OXC treatment, showing both good response to therapy and excellent tolerability.

Discussion

OXC is a new AED characterized by good efficacy and high tolerability in children with epilepsy.

Previous studies showed that OXC-monotherapy at daily doses of 15—20 mg/kg (approximately 900—1200 mg in adults) achieves complete seizure control in about 60% of previously untreated adults, adolescents, and children with partial epilepsy.[19,20] As far as efficacy is concerned, we did not find any significant differences as regards efficacy in patients affected by simple (50%), complex partial (90%), or secondarily generalized (80%) (Fig. 2).

Paradoxically, OXC can exacerbate abnormalities in EEG and frequency seizure in generalized or focal idiopathic epilepsy.[21,22] We have reported three cases of worsening in patients affected by focal idiopathic epilepsy but without EEG-abnormalities exacerbation. On the contrary, a normalization of EEG was observed in 25% of the cases.

A placebo-controlled, dose ranging trial performed by Barcs et al.[23] showed that the efficacy of OXC increases linearly in accordance with the drug dose. By medians of a statistical analysis, we also noticed an important correlation between the response to therapy and the dose expressed in mg/kg.

No clear-cut relationship between plasma drug concentration and clinical response was identified, and, at present, there are no clear indications for the routine monitoring of OXC plasma levels as a guide to dosage adjustment.[5,16] However, in our study we reported a correlation between MHD plasmatic levels and clinical outcome at T1, not confirmed in T2 and T3 probably because of the small number of cases evaluated. Further statistical analysis will be performed to evaluate this result in a higher number of patients.

The results of the analysis have shown a statistically significant correlation between MHD plasmatic levels and the dose expressed in mg/kg. This confirms a first order linear relationship between the two values, previously shown in drug pharmacokinetic studies.[5,24,25]

The incidence of hyponatraemia reported in a clinical study[26] is 2.5% and increasing with age, whereas, in our experience, a reduction of natraemia levels was not observed.

The Quality Standards and the Therapeutics and Technology Assessment Subcommittees of the American Academy of Neurology reported a percentage of discontinuation due to adverse events equal to 14%.[27,28]

In our study OXC tolerability is high: 75% of the patients did not present any side effects. In the remaining 25%, side effects were minor or moderate and decreasing at various controls. Among these, only hyperphagia has not been described in literature. Only one patient had to stop the treatment due to excessive sedation.

Both patients affected by symptomatic and by idiopathic epilepsy responded to OXC treatment. Seventy-two percent were idiopathic and 50% were symptomatic. Unfortunately, the number of children affected by symptomatic or cryptogenic epilepsy is not high enough to reach a conclusion. Anyway, in meta-analysis the response to OXC-monotherapy in adults with refractory epilepsy was similar (47%).[27,28] OXC could be indicated, in particular, for patients affected by idiopathic epilepsy characterized by high seizure frequency.

Idiopathic epilepsy is characterized by benign outcome and prompt response to antiepileptic drug.

Rolandic epilepsy, in particular, would not be treated if the patient presented few seizures and a good compliance by parents or caregivers. Ambrosetto et al.[29,30] suggested that anticonvulsant treatment could be delayed until the third seizure occurrence. It is reasonable to withhold anticonvulsant if the child and family are comfortable with this approach.[31,32]

Actually, in clinical practice, it is quite common to treat rolandic epilepsy, due to high seizure frequency (weekly or monthly) and parental anxiety.

The response is usually quite prompt and drug doses are not high in order to control seizures. However, in our study, to get an optimal clinical response it was necessary to increase the OXC dose even in patients with benign centro-temporal spikes.

Among the group of idiopathic epilepsy, we have enrolled seven patients with occipital epilepsy, who all resulted responders to treatment with OXC.

It becomes then primarily important to choose an effective, but also very well tolerated drug. In our experience, as in literature, OXC fulfils both these criteria.

Conclusion

OXC is effective and very well tolerated both in symptomatic and idiopathic epilepsy. We can therefore conclude that OXC can be considered a first line drug in children with epilepsy, particularly in the idiopathic form.

References

1. Bang L, Goa K. Oxcarbazepine: a review of its use in children with epilepsy. *Paediatr Drugs* 2003;**5**(8):557—73.
2. Schmidt D, Elger CE. What is the evidence that oxcarbazepine and carbamazepine are distinctly different antiepileptic drugs? *Epilepsy Behav* 2004;**5**(5):627—35.
3. McLean MJ, Schmutz M, Wamil AW, Olpe HR, Portet C, Feldmann KF. Oxcarbazepine: mechanism of action. *Epilepsia* 1994;**35**:S5—9.
4. Schmutz M, Brugger F, Gentsch C, McLean MJ, Olpe HR. Oxcarbazepine: pre-clinical anticonvulsivant profile and putative mechanism of action. *Epilepsia* 1994;**35**: S47—50.
5. Gonzalez-Esquivel DF, Ortega-Gavilan M, Alcantara-Lopez G, Jung-Cook H. Plasma level monitoring of oxcarbazepine in epileptic patients. *Arch med res* 2000;**31**:202—5.
6. Beydoun A, Sachdeo RC, Rosenfeld WE, et al. Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. *Neurology* 2000;**54**(12):2245—22451.
7. Sachdeo R, Beydoun A, Schachter SC, et al. Oxcarbazepine (Trileptal) as monotherapy in patients with partial seizures. *Neurology* 2001;**57**(5):864—71.
8. Schachter SC, Vazquez B, Fisher RS, et al. Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures. *Neurology* 1999;**52**(4):732—7.
9. Glauser TA, Nigro M, Sachdeo RC, et al. Adjunctive therapy with oxcarbazepine in children with partial seizures. *Neurology* 2000;**54**(12):2237—44.
10. Schmidt D, Sachdeo R. Oxcarbazepine for treatment of partial epilepsy: a review and recommendations for clinical use. *Epilepsy Behav* 2000;**1**(6):396—405.
11. Beydoun A, Sachdeo R, Kutluay E, McCague K, D'Souza J. Sustained efficacy and long-term safety of oxcarbazepine: 1-year open-label extension of a study in refractory partial epilepsy. *Epilepsia* 2003;**44**(9):1160—5.
12. Coppola G. Treatment of partial seizures in childhood: an overview. *CNS Drugs* 2004;**18**(3):133—56.
13. Albani F, Grassi B, Ferrara R, Turrini R, Baruzzi A. Immediate (overnight) switching from carbamazepine to oxcarbazepine monotherapy is equivalent to a progressive switch. *Seizure* 2004;**13**(4):254—63.
14. Kramer L. Clinical expert report on the clinical documentation Trileptal®, Novartis, data on file, Basle, 1998.
15. Ferrendelli JA. Concerns with antiepileptic drug initiation: safety, tolerability and efficacy. *Epilepsia* 2001;**42**(S4):28—30.

16. Perucca E. Clinical pharmacology and therapeutic use of the new antiepileptic drugs. *Fundam Clin Pharmacol* 2002;**15**(6):405—17. Review. Erratum in: Fundam Clin Pharmacol.
17. Hengel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. *Epilepsia* 2001;**42**(6):796—803.
18. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on classification and terminology of the international against epilepsy. *Epilepsia* 1989;**30**:389—99.
19. Sachdeo R, Edward K, Hasegawa H, et al. Safety and efficacy of oxcarbazepine 1200 mg/day in patients with recent onset partial epilepsy. *Neurology* 1999;**52**(S2):A391.
20. Schmidt D, Sachdeo R. Oxcarbazepine for treatment of partial epilepsy: a review and recommendations for clinical use. *Epilepsy Behav* 2000;**1**:396—405.
21. Gelisse P, Genton P, Kuate C, Pesenti A, Baldi-Moulinier A, Crespelle A. Worsening of seizures by oxcarbazepine in juvenile idiopathic generalized epilepsies. *Epilepsia* 2004;**45**(10):1282—6.
22. Chapman K, Holland K, Erenberg G. Seizure exacerbation associated with oxcarbazepine in idiopathic focal epilepsy of childhood. *Neurology* 2003;**61**(7):1012—3.
23. Barcs G, Walker EB, Elger CE, et al. Oxcarbazepine: placebo-controlled, dose-ranging trial in refractory partial epilepsy. *Epilepsia* 2000;**41**(12):1597—607.
24. Lloyd P, Flesch G, Dieterle W. Clinical pharmacology and pharmacokinetics of oxcarbazepine. *Epilepsia* 1994;**35**:S10—3.
25. Sallas WM, Milosavljev S, D'Souza J, Hossain M. Pharmacokinetic drug interactions in children taking oxcarbazepine. *Clin Pharmacol Ther* 2003;**74**(2):138—49.
26. Pellock JM. Tricyclic anticonvulsants: safety and adverse effects. *Epilepsy Behav* 2002;**3**:S19—23.
27. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs, I: treatment of new onset epilepsy. *Neurology* 2004;**62**:1252—60.
28. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs, II: treatment of refractory epilepsy: report of the TTA and QSS subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2004;**49**(5):410—23.
29. Ambrosetto G, Rossi PG, Tassinari CA. Predictive factors of seizure frequency and duration of anti-epileptic treatment in rolandic epilepsy: a retrospective study. *Brain Dev* 1987;**9**(3):300—4.
30. Ambrosetto G, Tassinari CA. Antiepileptic drug treatment of benign childhood epilepsy with rolandic spikes: is it necessary? *Epilepsia* 1990;**31**(6):802—5.
31. Ma CK, Chan KY. Benign childhood epilepsy with centrotemporal spike: a study of 50 Chinese children. *Brain Dev* 2003;**25**(6):390—5.
32. Hamada Y, Okuno T, Hattori H, Mikawa H. Indication for antiepileptic drug treatment of benign childhood epilepsy with centrotemporal spikes. *Brain Dev* 1994;**16**(2):159—61.